REMARKS

I. Status of the Claims

Claims 75-84 are pending in the application. Claims 75-84 have been rejected by the Examiner. Claim 75 has been amended to recite that phagocytosis is decreased such that not more than about 76% of particulate material is ingested. Support can be found in the Specification at least at page 1, lines 24-26; page 28, lines 31-34; and page 31, line 25 to page 32, line 14 and Table 2. Accordingly, no new matter has been introduced by this Amendment.

II. Claim Rejections Under 35 USC 112

The Examiner has rejected claims 75-84 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner argues that there is no support for the language "in the amount of at least 24%." Applicants respectfully traverse. As discussed in the previous response, basis for this amendment may be found in the Specification at page 31, line 21 in Table 2. However, in an effort to expedite prosecution, Applicants have amended claim 75 to recite that phagocytosis is decreased such that not more than about 76% of particulate material is ingested. Support can be found in the Specification at least at page 28, lines 31-34 and page 31, line 25 to page 32, line 14 and Table 2. Accordingly, claim 75 fully complies with the written description requirement and the rejection should be withdrawn.

III. Claim Rejections Under 35 USC 102

The Examiner rejected claims 75-84 under 35 U.S.C. 102(b) as allegedly being anticipated by JP 408143442 ("Matsuura") and as evidenced by Van der Ven et al., *Inactivation of Soybean Trypsin Inhibitors and Lipoxygenase by High Pressure Processing*, 53 J. AGRIC. FOOD CHEM. 1087-1092 (2005) ("Van der Ven") and Kwok et al., *Optimizing Conditions for Thermal Processes of Soy Milk*, 50 J. AGRIC. FOOD CHEM. 4834-4838 (2002) ("Kwok"). Applicants respectfully traverse this rejection.

As amended, the presently claimed invention relates to a topical method of decreasing phagocytosis or ICAM-1 expression in a patient having one or more of the conditions consisting of pulmonary emphysema, immunological lung disorders, periodontal disease, atherosclerotic plaques, Mid-dermal elastosis, pigmentation disorders, psoriasis, eczema and Acne vulgaris. The method comprises applying topically to an affected organ of said patient a therapeutically phagocytosis- or ICAM-1 decreasing effective amount of composition containing active trypsin inhibitory activity comprising a non-denatured soy extract having active trypsin inhibitory activity wherein said phagocytosis is decreased such that not more than about 76% of particulate material is ingested.

The Examiner relies upon Matsuura as teaching the addition of water to ground soybeans, heating the ground matter to a temperature of from 5 to 100°C, and then filtering the extract. The Examiner also argues that Matsuura uses the extract to treat eczema. First, Applicants note that Matsuura in no way relates to a topical method of decreasing phagocytosis or ICAM-1 expression in a patient. As discussed in the Specification, the presently claimed invention is based on the discovery that PAR-2-mediated phagocytosis and PAR-2 mediated ICAM expression can be specifically altered using the non-denatured soy extracts recited by the present claims. See, Specification page 13, lines 3-13. Such a method is neither taught nor suggested by Matsuura.

Further, Matsuura teaches that the external preparation for skin has an effect on preventing rough skin, curing hand eczema or housewives' eczema and preventing skin inflammation or itching caused by athlete's foot and the like. See page 8, end of paragraph [0011] and paragraph [0016] of the English Translation of Matsuura. As discussed in the Specification, disorders that can be treated or prevented using the instant invention include any disorder that can be ameliorated by either an increase or decrease in phagocytosis or ICAM-1 expression in appropriate cells. The rough skin and housewives' eczema conditions of Matsuura are much different from the conditions treated in the presently claimed invention. Indeed, Nanko, *Treatment of Housewives' Hand Eczema*, JMAJ 47(1): 44-51, 2004, specifically teaches that the term "housewives' eczema" is synonymous with "hand eczema" which is popularly called "sore hands" or "chapped hands" resulting from domestic

tasks. This "housewives' eczema" is quite different from the mid-dermal elastosis skin disorders treated by the presently claimed invention.

The Examiner recognizes that Matsuura does not teach or suggest that the soybean extracts described therein contain active soy trypsin inhibitor proteins. Indeed, Applicants again direct the Examiner's attention to the previously filed Declaration of Robert Zivin dated December 23, 2003. As set forth therein, exposure to high heat as described in each of the Matsuura examples, would denature and thus deactivate proteins such as STI. Accordingly, one of ordinary skill in the art, following Matsuura would, therefore, not expect that the Matsuura extract must be denatured, much less, necessarily obtain a soybean extract that contains non-denatured soy trypsin inhibitory activity. Accordingly, Matsuura cannot anticipate the present claims.

Nevertheless, the Examiner relies upon Matsuura as **inherently** describing Applicants claimed methods and relies upon Van der Ven and Kwok as teaching that soymilk contains trypsin inhibitor activity. According to the Examiner, because Kwok teaches that the extent of the destruction of trypsin inhibitor activity in soy milk for nutritive value or protein efficiency ratio was reported to be 90%, the soymilk of Kwok and Van der Ven must therefore have 10% trypsin inhibitor activity. The Examiner then argues that both Kwok and Van der Ven are evidence that the soybean extracts of Matsuura contain 10% trypsin inhibitor activity. Specifically, the Examiner argues that Kwok in Figure 1 shows that at 120°C, 90% inactivation of TIA occurs after more than 400 seconds or more than 6 ½ minutes. Therefore, according to the Examiner, based upon the teachings of Kwok and Van der Ven the 120°C heat treatment of 3 minutes of Matsuura allegedly would not have reasonably been expected to reach 90% inactivation leaving more than 10% of the original soybean trypsin inhibitor. Applicants respectfully disagree.

As the Examiner is well aware, demonstrating inherency "requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trintec Industries, Inc. v. Top-U.S. Corporation*, 295 F.3d 1292, 1295 (Fed. Cir. 2002). As discussed above and as is clear from the Zivin Declaration, one of ordinary skill in the art following Matsuura, would not necessarily obtain a soybean extract that contains non-

denatured soy trypsin inhibitory activity. Additionally, just because a soy extract is not 100% inactivated for nutritional optimization does not in any way mean that it will always and necessarily function to inhibit phagocytosis.

Applicants refer the Examiner to the attached Declaration of Connie Baozhen Lin ("Lin Declaration"). As demonstrated therein, two edible soymilk preparations not only failed to inhibit phagocytosis, but actually enhanced this process. In contrast, a non-denatured soybean extract according to the claimed invention was able to inhibit SLIGLR-induced phagocytosis to about the same level as the positive control. Accordingly, even if, as the Examiner argues, the edible soymilk preparations such as disclosed by Kwok and Van der Ven contain active soybean trypsin inhibitor activity, they do not inhibit phagocytosis and therefore do not read on the non-denatured soy extract used in the claimed method. Further, even if one of ordinary skill in the art were to somehow read Matsuura as teaching soy extracts containing 10% soybean trypsin inhibitor activity, the use of the soy extracts of Matsuura cannot anticipate the method of decreasing phagocytosis or ICAM-1 expression using the soy extracts recited by the present claims.

The Examiner however, takes the position that because the Declaration of Yaping Hu dated June 30, 2010 ("Hu Declaration") states that the error bars of the different measurements taken in Table 1 were as high as +/- 15%, it follows that "sample K has STI inhibitory activity anywhere from 15.2-30%" and therefore reads on 24%. Applicants respectfully disagree. The statement in the Hu Declaration regarding error bars of ±15% have been misconstrued by the Examiner. The discussion refers to the data set forth in Table 2. As discussed therein, "when the biological activity (inhibition of phagocytosis) was measure at the time of patent application, the error bars of the different measurements were as high as +/- 15%. These data further suggest that activities at or below 15% do not represent real biological activity but a technical threshold." This in no way should be interpreted as a suggestion that for each value given for any calculation relating to this invention one should add or subtract 15%. As demonstrated by Table 1 and Table 2 of the Hu Declaration and stated therein at paragraph 4, "Because of this assay variability, results of this assay that are at or below 18-20% are considered as below the margins of detection of the reliable threshold

to describe real biological activity." In fact, Table 3 demonstrates that soy preparations made according to Matsuura "showed no trypsin inhibitory activity above this cutoff [18-20%], documenting that they lack trypsin inhibitory activity." In contrast, the soy preparations of the present application at "1% concentration, had inhibitory activity of 57.9%. This is much higher than the 18-20 cutoff, which is considered as 'noise' and is not believed to be related to real activity."

In the Office Action, the Examiner states "Clearly the results in the declaration are inconclusive since three different assays yielded three different results as shown in Table 1 of the Hu declaration." Applicants are grateful that the Examiner recognizes this important point with respect to the trypsin inhibition assay. As stated in the Hu Declaration, paragraph 4:

> "The tryspin inhibition assay described above has some limitations. When the same preparation is tested with the same assay, independently, at different times, the results are not identical but appear within a range, which is a situation more commonly observed for samples with low inhibitory activity. For example, when the same pure STI preparation from Signa was tested three times independently, using the same batch, same concentration and same assay, the results that were obtained varied, as shown in Table 1 below. Because of this assay variability, results of this assay that are at or below 18-20% are considered as below the margins of detection of the reliable threshold to describe real biological activity."

Accordingly, the Hu Declaration clearly demonstrates that soy preparations made according to Matsuura have minimal to no trypsin inhibition activity and therefore are not non-denatured soy extracts having active trypsin inhibitory activity which are required in the presently claimed method. Further, as discussed above and as demonstrated by the Lin Declaration, the use of the soy extracts of Matsuura cannot anticipate the method of decreasing phagocytosis or ICAM-1 expression using the soy extracts recited by the present claims. Accordingly, for all these reasons, Matsuura, even as evidenced by Kwok and Van der Ven, fails to anticipate the present claims.

IV. Claim Rejections Under 35 USC 102/103

The Examiner has also rejected claims 75-84 under 35 U.S.C. 102(b) as allegedly anticipated by or, in the alternative, under 35 U.S.C. 103(a) as allegedly obvious over Matsuura and as evidenced by Van der Ven and Kwok. Applicants respectfully traverse this rejection. For the reasons discussed above, Applicants maintain that the Examiner has failed to establish that the presently claimed invention is anticipated by Matsuura even "as evidenced by" Kwok or Van der Ven. There is no teaching or suggestion of a method of decreasing phagocytosis or ICAM-1 expression using a non-denatured soy extract having active trypsin inhibitory activity wherein phagocytosis is decreased such that not more than about 76% of particulate material is ingested. Further, Matsuura fails to render the presently claimed invention obvious.

In the Office Action, the Examiner argues that:

> …even if the claimed extract composition is not identical to the referenced extract composition with regard to some unidentified characteristics, the differences between that which is disclosed and that which is claimed are considered to be so slight that the referenced extract composition is likely to inherently possess the same characteristics f the claimed extract composition. Thus, the claimed extract composition would have been obvious to those of ordinary skill in the art within the meaning of USC 103. [Office Action, p. 8]

Applicants respectfully disagree. The differences between the extracts disclosed by Matsuura and the extracts used in the presently claimed method are not "slight." Nowhere does Matsuura mention that the soybean extracts described therein contain active soy trypsin inhibitor proteins or a method of decreasing phagocytosis or ICAM-1 expression. Further, there is nothing in the teachings of Kwok or Van der Ven that would provide one of ordinary skill in the art with the motivation or guidance to modify the Matsuura extracts in such a way that the soy extracts would have active trypsin inhibitory activity wherein said phagocytosis is decreased such that not more than about 76% of particulate material is ingested. Indeed, Matsuura, Kwok and Van der Ven provide no teaching or suggestion that the percent of ingestion or active trypsin activity would have any effect on the treatment of conditions consisting of consisting of pulmonary emphysema, immunological lung disorders, periodontal disease, atherosclerotic plaques, Mid-dermal elastosis, pigmentation disorders,

psoriasis, eczema and Acne vulgaris. In fact, Kwok relates to a mathematical model developed in order to predict the optimal time-temperature combination to process soy foods, to achieve maximal bacterial destruction, maximal TIA inactivation and minimal deterioration in nutritional and sensory qualities. Accordingly, there would simply be no motivation to increase the percent of active trypsin inhibitory activity and the presently claimed invention is not obvious in view of Matsuura. Applicants therefore, respectfully request that this rejection be withdrawn.

V. Claim Rejections Under 35 USC 103

The Examiner has rejected claims 75-84 as allegedly unpatentable over Matsuura as evidenced by Van der Ven and Kwok. Applicants respectfully traverse this rejection.

The Examiner argues that

> In the event it is seen that the inhibitory activity claimed of at least about 24% is not reached by Matsuura it is noted that in Matsuura and the declaration that sample K (which was used in Matsuura) had 15.2% activity and the specification shows the results for the % ingestion are always calculated plus or minus 11-15 (this is also true for % inhibition as shown on table 2 of the declaration) thus the results can come out unclear and since such is the case it is obvious to yield plus or minus 15 which will make the % of inhibition within the range claimed it is also obvious since to use amounts which yield plus or minus 15% inhibition of trypsin inhibitory activity is well within the range of the ordinary artisan in an effort to optimize the desired results. [Office Action, p. 11]

It appears that the Examiner is taking the position that because the % Ingestion in Table 2 on page 32 of the specification was 76% +/- 15 for STI, 0.01% and 41.6% +/- 11 for STI, 1% that, one would always add or subtract 11-15% from the % inhibition or % ingestion. The Examiner then concludes that since the Hu Declaration states that Sample K has 15.2% inhibition, when you add 15% it falls within the claimed range of 24% inhibition or 76% ingestion.

The Examiner also argues that a prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a prima facie case of obviousness. However, Matsuura in no way teaches a range of ingestion inhibitory activity that encompasses the percent ingestion or trypsin inhibitory activity recited in presently claimed method, much less, that % ingestion or trypsin inhibitory activity would have any effect on the conditions recited by the present claims. Indeed, nowhere does Matsuura mention that the soybean extracts described therein contain active soy trypsin inhibitor proteins. Further, there is nothing in the teachings of Kwok or Van der Ven that would provide one of ordinary skill in the art with the motivation or guidance to modify the Matsuura extracts in such a way that the soy extracts would have active trypsin inhibitory activity wherein said phagocytosis is decreased such that not more than about 76% of the particulate material is ingested. Further, Matsuura, Kwok and Van der Ven, taken alone or in any combination, fail to provide any teaching or suggestion that the percent of active trypsin activity or particulate material ingested would have any effect on the treatment of conditions consisting of pulmonary emphysema, immunological lung disorders, periodontal disease, atherosclerotic plaques, Mid-dermal elastosis, pigmentation disorders, psoriasis, eczema and Acne vulgaris. Accordingly, there would simply be no motivation to increase the percent of active trypsin inhibitory activity or to specifically alter PAR-2 mediated phagocytosis or PAR-2 mediated ICAM expression using a non-denatured soy extract. Indeed, none of the references relied upon by the Examiner, taken alone or in any combination, teach or suggest a method of decreasing phagocytosis or ICAM-1 expression using the soy extracts as recited by the present claims. Accordingly, Matsuura fails to render the presently claimed method obvious and the rejection should be withdrawn.

VI. Conclusion

For the reasons set forth above, Applicants respectfully request withdrawal of all outstanding objections and rejections and that a timely Notice of Allowance is issued in this case.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 10-0750/JPB0438US/ALC. If a fee is required for an Extension of time 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account No. 10-0750/JBP0438US/ALC.

Respectfully submitted,

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